REMARKS

I. Support for the Amendments to the Specification and the Claims

The specification has been amended to correct the title of the paragraph reciting the cross-references to related applications. No new matter is added by virtue of the amendments to the specification.

Claims 1-13, 29-31, and 54-64 were previously in the application, along with withdrawn claims 14-28.

Claims 1, 3-4, 6-9, 11-13, 29-30, 54, 56-67, 60-62, and 64 have been amended, claims 5, 10, 31, and 63 have been canceled, and new claims 65-81 have been added. Claims 5, 10, 31, and 63 have been canceled without prejudice to their pursuit in an appropriate divisional or continuation application. Claims 14-28 and 32-41 are withdrawn. Claims 1-4, 6-9, 11-13, 29-30, 54-62, and 64-81 are currently in the application.

Support for the amendments to claims 1, 3-4, 6-9, 11-13, 29-30, 54, 56-67, 60-62, and 64 and for new claims 65-81 can be found in the specification, figures, and claims as originally filed. No new matter has been added by virtue of the amendments to the claims.

Additional support for the amendments to claims 1, 3-4, 6-9, 11-13, 29-30, 54, 56-67, 60-62, and 64 and for new claims 65-81 can be found in the language of original claims 1-13 and from page 3, line 19, to page 4, line 6; on page 5, lines 5-13; from page 5, line 23, to page 10, line 11; in the Examples; and in the Figures.

II. Status of the Claims

Claims 1-28 were previously in the application. The claims were subject to an

Election/Restriction Requirement, and claims 1-13 (Group I) were elected with traverse.

Claims 1-13, 29-31, and 54-64 were previously in the application. Claim 1 had been amended, and new claims 29-53 had been added. Claims 14-28 were previously withdrawn Claims 1-2 and 30 had been amended, previously withdrawn claims 42-53 had been cancelled, and new claims 54-64 had been added to the present application. Previously withdrawn claims 42-53 had been cancelled without prejudice to their pursuit in an appropriate divisional or continuation application. Claims 14-28 and 32-41 were withdrawn.

Claims 1-13, 29-31, and 54-64 were previously in the application, along with withdrawn claims 14-28.

Claims 1, 3-4, 6-9, 11-13, 29-30, 54, 56-67, 60-62, and 64 have been amended, claims 5, 10, 31, and 63 have been canceled, and new claims 65-81 have been added. Claims 5, 10, 31, and 63 have been canceled without prejudice to their pursuit in an appropriate divisional or continuation application. Claims 14-28 and 32-41 are withdrawn. Claims 1-4, 6-9, 11-13, 29-30, 54-62, and 64-81 are currently in the application.

III. The Priority Claim is Acknowledged

Applicants thank the Examiner for acknowledging the priority claim. Applicants were merely requesting an acknowledgement of the priority claims to U.S. Provisional Application 60/485,509 (filed July 6, 2003) and U.S. Provisional Application 60/485,607 (filed July 7, 2003).

IV. The Drawings are Accepted

Applicants thank the Examiner for accepting the drawings.

V. The Restriction Requirement

With respect to Applicants' previous remarks concerning the Restriction Requirement, Applicants wish to note that they had been requesting a consideration of rejoinder of claims in the event that the remaining claims had been allowable. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call Applicants' undersigned representative as soon as convenient.

VI. The Objection to Claim 1 is Rendered Moot

The Examiner has objected to claim 1 for the misspelling of the word "hematopoietic" in the last line of the claim. Applicants thank the Examiner for drawing this matter to their attention, but note that this objection has been rendered moot due to the deletion of this particular instance of this word in claim 1.

VII. The Rejection of Claims 1-13 and 29-31 under 35 U.S.C. §112, First Paragraph, is Traversed in Part, Accommodated in Part, and Rendered Moot in Part

The Examiner has rejected claims 1-13 and 29-31 under 35 U.S.C. §112, first paragraph, for alleged failure to comply with the written description requirement and for alleged new matter based on the previous amendments to the claims. Applicants have further amended the language of claim 1 in particular.

However, the Patent Office alleges, in pertinent part:

> The working example does not appear to be an embodiment of the claimed invention, since there is no mention of cell cycle within the working examples. [P. 4.]

Applicants respectfully draw the Examiner's attention to the following description of the protocol for the Examples:

> In an exemplary embodiment, the methods of the invention (when applied to murine cells) comprise the culture of unseparated or purified LRH marrow stem cells (or unseparated marrow). Specifically LRH cells are cultured in DMEM with 15% fetal calf sera and steel factor (50 ng/ml), Flt-3 (100 ng/ml), and thrombopoietin in Teflon bottle cultures at 37°C, 5% CO2. Under these conditions, primitive stem cells progress through cell cycle in a highly synchronous fashion. These cells are then harvested at about 32 hours (mid S-phase) or 40 hours (late S-phase), washed, and subcultured in DMEM, 15% fetal calf sera, and GM-CSF, G-CSF, and steel factor (50 ng/ml) and differentiated cell production evaluated out to 14 days of subculture. See Figure 1 for a schematic representation. When 32 hour primary cultured cells are resubcultured, there is a marked increase in megakaryocyte production, while when 40 hour primary cultured cells are resubcultured, a marked increase in granulocytes is seen. These primary time points are referred to herein as megakaryocyte and granulocyte "hotspots", respectively, and the differentiated hematopoietic cells resulting from these subcultures are referred to herein as "32 hour hotspot cells" and "40 hour hotspot cells", respectively. [P. 6, l. 26 – p. 7, l. 8.]

Claims 3-4, 6-9, 13, and 29-30 are dependent on claim 1 and the same reasoning applies to these claims as well.

Claims 5, 10, and 31 have been cancelled and amended claims 11-12 are now dependent on new claim 68, thereby rendering the rejection moot with respect to those claims.

Applicants respectfully submit that remaining claims 1-4, 6-9, 11-13 and 29-30 fulfill the requirements of 35 U.S.C. §112, first paragraph, thereby placing these claims in condition for allowance, and request the Examiner's reconsideration accordingly.

VIII. The Rejection of Claims 1-13, 29-31, and 54-64 under 35 U.S.C. §112, Second Paragraph, is Traversed in Part, but Accommodated in Part

The Examiner has rejected claims 1-13, 29-31, and 54-64 under 35 U.S.C. §112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter.

Applicants respectfully disagree, but have amended claims 1 and 54 to further prosecution in a timely manner, but again respectfully draw the Examiner's attention to the following description in the specification:

> In an exemplary embodiment, the methods of the invention (when applied to murine cells) comprise the culture of unseparated or purified LRH marrow stem cells (or unseparated marrow). Specifically LRH cells are cultured in DMEM with 15% fetal calf sera and steel factor (50 ng/ml), Flt-3 (100 ng/ml), and thrombopoietin in Teflon bottle cultures at 37°C, 5% CO2. Under these conditions, primitive stem cells progress through cell cycle in a highly synchronous fashion. These cells are then harvested at about 32 hours (mid S-phase) or 40 hours (late S-phase), washed, and subcultured in DMEM, 15% fetal calf sera, and GM-CSF, G-CSF, and steel factor (50 ng/ml) and differentiated cell production evaluated out to 14 days of subculture. See Figure 1 for a schematic representation. When 32 hour primary cultured cells are resubcultured, there is a marked increase in megakaryocyte production, while when 40 hour primary cultured cells are resubcultured, a marked increase in granulocytes is seen. These primary time points are referred to herein as megakaryocyte and granulocyte "hotspots", respectively, and the differentiated hematopoietic cells resulting from these subcultures are referred to herein as "32 hour hotspot cells" and "40 hour hotspot cells", respectively. [P. 6, l. 26 – p. 7, l. 8.]

With respect to the Applicants' previous discussion of "reversible differentiation" and "cellular de-differentiation," the discussion in the Amendment and Declaration addressed the allegations of the Patent Office with respect to the previous rejection of claim 30 and confirmed that "reversible differentiation" ("cellular de-differentiation") was known in the art at the time when the invention was made. Applicants are somewhat perplexed by the continued rejection of claim 30 with respect to this point.

Claims 3-4, 6-9, 13, and 29-30 are dependent on claim 1 as an underlying claim, and claims 55-62 and 64 are dependent on claim 54 as an underlying claim, and the same amendments apply to these claims, respectively, as well. Claims 3-4, 6-9, 11-13, 29-30, 56-57, 60-62, and 64 have also been amended individually.

Claims 5, 10, 31, and 64 have been cancelled and amended claims 11-12 are now dependent on new claim 68, thereby rendering the rejection moot with respect to those claims.

Applicants respectfully submit that remaining claims 1-4, 6-9, 11-13, 29-30, 54-62, and 64 fulfill the requirements of 35 U.S.C. §112, second paragraph, thereby placing these claims in condition for allowance, and request the Examiner's reconsideration accordingly.

VIII. The Rejection of Claims 1-4, 13, and 29-31 Under 35 U.S.C. §102(b) over Hagihara is Traversed in Part and Rendered Moot in Part

The Examiner has maintained the rejection of claims 1-4, 13, and 29-31 under 35 U.S.C. §102 for alleged anticipation by Hagihara et al. (J. Immunol. Methods 253: 45-55 [2001]). Applicants traverse the rejection and respectfully request reconsideration of these claims.

Claim 31 has been cancelled, and the rejection is rendered moot with respect to that claim.

The Patent Office alleges in pertinent part:

> Applicant alleges that Hagihara lacks sufficient detail as to the timing of the culturing to anticipate the claims. See page 16. The examiner disagrees; for the ample reasons set forth above, the limitations of claim 1 fail to effectively describe the "timing" conditions, much less to limit them such that they

> overcome the art. The examiner also wishes to note respectfully that claim 1 does not require culturing only purified BMSCs in step (a), since the method itself **comprises** the five steps. Additional cells may be included in step (a). See M.P.E.P. § 2111.03.
>
> Applicant alleges that Hagihara "discloses a vague, imprecise, and random period of time," but as discussed above, the claim limitations themselves are vague and imprecise. There are no clear criteria for selecting a phase of the cell cycle and no requirements that the contact with the growth factor or cytokine occur only at some "predetermined" cell cycle phase -- again, claim 1 is drawn to a method **comprising** five steps, so additional culturing steps are reasonably included within its scope.
>
> The examiner has fully considered the declaration submitted under 37 C.F.R. 1.132 by Peter Quesenberry (hereafter "the Quesenberry declaration"), but it is not persuasive of error. The Quesenberry declaration contains no data, so it constitutes opinion evidence. M.P.E.P. § 716.01(c) provides guidelines for assessing expert opinion evidence. In this case, the declaration seeks to establish that the prior art reference did not recognize certain features of the steps within its method, but as described above, such a consideration is immaterial to patentability. The declaration is wholly unsupported by factual evidence, and the declarant is the inventor, so it is reasonable to presume that he has an interest in the outcome of the case. The declaration appears to state only conclusions, so it cannot overcome the anticipation rejection, especially given the vague and indefinite nature of the claims. Furthermore, the Quesenberry declaration shares no nexus with the instant claims. See M.P.E.P. § 716.01(b). The Quesenberry declaration refers to a "link" between particular phases of the cell cycle and particular cell types. See page 8. However, there is no such "link" recited or fairly implied by the claims. Since applicant's comments appear to be a substantial reiteration of the statements in the Quesenberry declaration, the examiner's points above also apply to the declaration. [Pp. 14-15; all emphasis in original.]

Applicants respectfully disagree. The assertion of the inherency argument by the Patent Office in clearly inapropos. Regardless of whether the initial culture of Hagihara might become synchronous, the fact remains that the subculturing step took place only "every week" without regard to the cell cycle phase of the cells being treated to induce DC formation.

Even if it were possible to know the duration of the cell cycle in numbers of hours (and it is not), Hagihara's vague, imprecise, and random "every week" neither discloses nor suggests a consistently specific cell cycle phase.

Applicants respectfully submit, therefore, that it cannot be concluded by one of ordinary skill in the art that Hagihara subcultured synchronously cycled cell cultures with a growth factor or cytokine "at a predetermined phase of the cell cycle."

Solely in the interests of furthering prosecution in a timely manner, Applicants have directed claim 1 to "mid-S phase." Nothing in Hagihara discloses or suggests contacting the synchronous cells at mid-S phase or at any other specific phase of the cell cycle.

The Patent Office alleges that "the limitations of claim 1 fail to effectively describe the 'timing' conditions" [p. 14], but this is part and parcel of the point Applicants have been making – namely, because there is ***no* discussion of cell cycle in Hagihara**, one of skill in the art is left ***only* with a vague reference to timing (i.e., "every week"), *rather than* cell cycle phase**. Such a vague reference cannot anticipate step b of amended claim 1 (or former step d of claim 1), because it does not confirm that, from one week to the next, each group of cells would consistently be subcultured at the same phase in the cell cycle. Whether "timing" is measured by the clock or by the cell cycle, it is abundantly clear that the vague "every week" of Hagihara fails to disclose or suggest a given phase of the cell cycle as claimed in the present invention.

Moreover, whether or not the use of "comprising" with respect to the method means that any additional culturing steps might be added to **claim 1**, the Patent Office cannot add additional steps to **Hagihara** in an effort to supply the deficiencies of Hagihara and encompass all the limitations of claim 1. In addition, it is the "method" – not the "cells" – that is "comprising" a series of steps. In the language of claim 1, the present participle "comprising" modifies the noun "method." Finally, an additional step of adding cells other than purified bone marrow stem cells would be contrary to the limitations of step a) and step b).

With respect to the Declaration by Dr. Quesenberry ("Declaration"), the Patent Office seems to have discounted it, in part because the Declarant is an inventor and in part because the Declaration contained no data. The Examiner's attention is drawn to the attached Colvin reference (Colvin et al., "Heterogeneity of Non-Cycling and Cycling Synchronized Murine Hematopoietic Stem/Progenitor Cells," J. Cell. Physiol. 222: 57-65 (2010); "Colvin"). Colvin had not yet been published when the previous Amendment and Declaration were filed.

Colvin provides data confirming cell differentiation relative to cell cycle (see, e.g., Figures 2-3). The Examiner's attention is particularly drawn to Tables 2-3 and to Figures 5-7 (pp. 63-64). This work as now been published.

Claims 2-4, 13, and 29-30 are directly or indirectly dependent on claim 1 as an underlying claim, and the arguments and limitations of claim 1 apply to claims 2-4, 13, and 29-30 as well. With respect to claims 29-30, Hagihara makes no mention of a differentiation hotspot.

Applicants respectfully submit that remaining claims 1-4, 13, and 29-30 fulfill the requirements of 35 U.S.C. §102(b), thereby placing these claims in condition for allowance, and request the Examiner's reconsideration accordingly.

IX. The Rejection of Claims 1-6, 10-11, 13 and 29-31 under 35 U.S.C. §103(a) over Hagihara Taken with Yan and Messner is Traversed, but Rendered Moot in Part

The Examiner has rejected claims 1-6, 10-11, 13, and 29-31 under 35 U.S.C. 103(a) as unpatentable over Hagihara et al. (J. Immunol. Methods 253: 45-55 [2001]) in view of Yan et al. (Blood, 96(11; part 1): 680a (November 2000) ("Yan")); and Messner et al. (Blood 70(5): 1425-1432 (November 1987) ("Messner")). Applicants traverse the rejection and respectfully request reconsideration of these claims.

Claims 5, 10, and 31 have been cancelled without prejudice, and claim 11 has been amended to be dependent on new claim 68 as an underlying claim. The rejection is moot with respect to these claims.

The Patent Office alleges in pertinent part:

> Hagihara does not explicitly teach that the culturing of cells in the presence of steel factor (SCF), thrombopoietin (TPO) and FLT-3 ligand (FLT3) promotes synchronous progression of the cells through the cell cycle. Hagihara does not indicate that the growth factor must be added during any particular cell cycle phase (although, as discussed above, the claims also make no such requirement; see M.P.E.P. § 2111.03).
>
> Yan teaches that the combination of factors SCF, TPO and FLT-3 in the culture medium stimulates the hematopoietic bone marrow cells to enter into synchronous cell cycle from resting state. For example, see the abstract of Yan, which clearly discloses that the purified bone marrow cells were quiescent (non-diving or "resting" at GO/G1 phase) at the beginning of the culture, that the addition of cytokines SCF, TPO and FLT- 3 stimulated the cells to enter into the cycle, and that the amount of synchronous cells in S phase increased during culturing in the presence of cytokines SCF, TPO and FLT-3.
>
> Messner teaches that cell cycle studies and stem cell engraftment studies indicate that the higher than normal proportions of multipotential hematopoietic cells are present in S phase during progression of the hematopoietic cells through the cell cycles. See abstract, e.g.
>
> A person of ordinary skill in the art would have had a reasonable expectation of success in synchronizing the BMSCs of Hagihara using Hagihara's medium containing SCF, TPO, and FLT-3 ligand because Yan teaches that such a medium promotes synchronous progression through the cell cycle. The skilled artisan would have been motivated to synchronize the cells in order to obtain more consistent results from the culturing step, especially given Messner's teaching that the cell cycle phase affects the proportion of multipotential cells in a population.
>
> The skilled artisan would have had a further reasonable expectation of success in synchronizing the cells and adding growth factor or cytokine (in this case, the GM-CSF of Hagihara) at various phases of the cell cycle because Messner teaches that more hematopoietic stem cells are at S phase than other cell cycle phases. The skilled artisan would have been motivated to determine the differentiability of Hagihara's stem cells at various points in the cell cycle in order to maximize the number of stem cells available for Hagihara's differentiation protocol. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that

> instance the fact that a combination was obvious to try might show that it was obvious under §103." *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1397 (U.S. 2007). In this case, there are only a few different points in the cell cycle, and Messner teaches that these points were well known at the time of the invention; testing stem cells at each of these points to identify their propensity for differentiation would have constituted routine experimentation at the time of the invention.
>
> It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to synchronize the cells of Hagihara with the medium of Hagihara and Yan and then to treat the synchronized cells at various points within the cell cycle in order to determine the optimal conditions for Hagihara's differentiation method. [Pp. 17-19; all emphasis in original.]

Hagihara has been discussed at length above, in the Declaration and throughout prosecution, and the same reasoning applies here. As discussed at length in the Declaration (mailed 12 June 2009), at the time the invention was made, the skilled artisan would have assumed that stem cells would be homogeneous and clonal in nature – not heterogeneous and giving rise to diverse cell types based on the phase of the cell cycle at which they were stimulated, as shown in the present invention. As a result, one of skill in the art would not have been motivated to treat stem cells at different phases of the cell cycle, because one of skill in the art would have had no reasonable expectation of any difference in the subsequent differentiation of cell types.

Yan and Messner, taken either alone or in combination together, fail to supply the deficiencies of Hagihara.

Both Yan and Messner have been discussed at length throughout prosecution, and the previous remarks apply here.

As noted in the Declaration (mailed 12 June 2009) with respect to Messner, this work is irrelevant to the present invention, as it found variations in frequencies of clonogenic precursors in the normal donor population, but also included marrow from leukemic patients, which cannot be equated with normal marrow. The cell cycle was addressed primarily to

determine the proportion of clonogenic precursors in S-phase by preincubation with tritiated thymidine, rather than synchronizing the cell cycles or by exposure of a synchronous population of stem cells "at a predetermined phase of the cell cycle." Messner fails to describe or suggest the claimed method of selecting a phase in the cell cycle to yield cell cycle specific cells, as discussed in the Declaration.

Nor would one of ordinary skill in the art be motivated to combine Hagihara, Yan, and Messner to arrive at the present invention. The present invention is not a combination, simple substitution, or improvement of known elements or methods to yield a predictable result. One of ordinary skill in the art would not have considered it "obvious to try" with any reasonable expectation of success. The unpredictability of the present invention goes far beyond a combination, simple substitution, or improvement of known elements or methods and would not have been "obvious to try."

Applicants note that claim 1 is an underlying claim for claims 2-4, 6, 13 and 29-30 and that the arguments that apply to claim 1 also apply to these claims.

Applicants respectfully submit that remaining claims 1-4, 6, 11, 13 and 29-30 fulfill the requirements of 35 U.S.C. §103(a), thereby placing these claims in condition for allowance, and request the Examiner's reconsideration accordingly.

X. The Rejection of Claims 7-9, 12, and 54-63 under 35 U.S.C. §103(a) over Hagihara, Yan, and Messner and Further in View of Klabusay and Ramsfjell is Traversed, but Rendered Moot in Part

The Examiner has rejected claims 7-9, 12, and 54-63 under 35 U.S.C. 103(a) as unpatentable over Hagihara et al. (J. Immunol. Methods 253: 45-55 [2001]); Yan et al. (Blood, 96(11; part 1): 680a (November 2000) ("Yan")); and Messner et al. (Blood 70(5): 1425-1432 (November 1987) ("Messner")); and further in view of Klabusay et al. (Blood

100(11): 4118 (November 2002) ("Klabusay")); and Ramsfjell et al. (Blood 88(12): 4481-4492 (December 1996) ("Ramsfjell")). Applicants traverse the rejection and respectfully request reconsideration of these claims.

Claim 63 has been cancelled without prejudice, and claim 12 has been amended to be dependent on new claim 68 as an underlying claim. The rejection is moot with respect to these claims.

The Patent Office alleges in pertinent part:

> Hagihara does not teach culturing in G-CSF. Hagihara does not teach all of the end points in claims 7-9, 12, and 54. Hagihara does not discuss the markers in claim 64.
>
> Klabusay teaches that hematopoietic stem cells are able to regenerate hematopoiesis in all lineages and that addition of G-CSF to their medium will significantly increase the number of maturated cells including granulocytes. See abstract, e.g.
>
> Ramsfjell teaches that culturing stem cells in SCF enhances megakaryocyte differentiation, as well as production of granulocytes and other mature hematopoietic cell types. See abstract, e.g. Ramsfjell teaches that when megakaryocytes mature, they produce platelets. *Id.*
>
> A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the G-CSF of Klabusay or the SCF of Ramsfjell for the GM-CSF of Hagihara in Hagihara's method taken in view of Yan and Messner because Klabusay and Ramsfjell teach that G-CSF and SCF affect the differentiation of Hagihara's cells. The skilled artisan would have been motivated to make such a substitution to determine whether Hagihara's method can be used with Klabusay's and Ramsfjell's growth factors/cytokines to direct differentiation to the endpoints already associated by Klabusay and Ramsfjell with those growth factors/cytokines. Varying Hagihara's method using these two different growth factors/cytokines and assaying for directed differentiation to the limited outcomes taught by Klabusay and Ramsfjell would have constituted routine experimentation at the time of the invention. See KSR at 1397.
>
> It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to vary the growth factor/cytokine in Hagihara's differentiation method in order to identify the effects of such variance on that method because Klabusay and Ramsfjell identified links between various growth factors and particular differentiation endpoints. [Pp. 19-21; emphasis in original.]

Applicants respectfully request clarification of the remark concerning claim 64, as claim 64 is not stated to have been rejected over this combination of references.

Hagihara has been discussed at length above, in the Declaration and throughout prosecution, and the same reasoning applies here. As discussed at length in the Declaration (mailed 12 June 2009), at the time the invention was made, the skilled artisan would have assumed that stem cells would be homogeneous and clonal in nature – not heterogeneous and giving rise to diverse cell types based on the phase of the cell cycle at which they were stimulated, as shown in the present invention. As a result, one of skill in the art would not have been motivated to treat stem cells at different phases of the cell cycle, because one of skill in the art would have had no reasonable expectation of any difference in the subsequent differentiation of cell types.

Yan, Klabusay, Ramsfjell, and Messner, taken either alone or in combination together, fail to supply the deficiencies of Hagihara.

Yan, Messner, Klabusay, and Ramsfjell have been discussed at length throughout prosecution, and the previous remarks apply here.

With respect to Klabusay and Ramsfjell, Applicants respectfully submit that while these references may disclose the generation of various hematopoietic lineages, neither of these references, either alone or in combination with each other or with Hagihara and/or Yan, discloses or suggests the present invention.

Nor would one of ordinary skill in the art be motivated to combine Hagihara, Yan, Klabusay, Ramsfjell, and Messner to arrive at the present invention. The present invention is not a combination, simple substitution, or improvement of known elements or methods to yield a predictable result. One of ordinary skill in the art would not have considered it "obvious to try" with any reasonable expectation of success.

Thus, the unpredictability of the present invention goes far beyond a combination, simple substitution, or improvement of known elements or methods and would not have been "obvious to try."

Applicants note that claim 1 is an underlying claim for claims 7-9 and 54-63 and that the arguments that apply to claim 1 also apply to these claims.

Applicants respectfully submit that remaining claims 7-9, 12, and 54-62 fulfill the requirements of 35 U.S.C. §103(a), thereby placing these claims in condition for allowance, and request the Examiner's reconsideration accordingly.

XI. The Rejection of Claim 64 under 35 U.S.C. §103(a) over Hagihara, Yan, Messner Klabusay, and Ramsfjell and Further in View of Herzog is Traversed

The Examiner has rejected claim 64 under 35 U.S.C. 103(a) as unpatentable over Hagihara et al. (J. Immunol. Methods 253: 45-55 [2001]); Yan et al. (Blood, 96(11; part 1): 680a (November 2000) ("Yan")); Messner et al. (Blood 70(5): 1425-1432 (November 1987) ("Messner")); Klabusay et al. (Blood 100(11): 4118 (November 2002) ("Klabusay")); and Ramsfjell et al. (Blood 88(12): 4481-4492 (December 1996) ("Ramsfjell")) as applied to claims 1-13, 29-31, and 54-63 above and further in view of Herzog et al. (Blood, 102: 3483-3493 (2003) ("Herzog")). Applicants traverse the rejection and respectfully request reconsideration of these claims.

The present application is a 35 U.S.C. §371 national stage of PCT application PCT/US2004/021637, filed July 6, 2004, which claims the priority benefit of U.S. Provisional Application Serial No. 60/485,509, **filed July 6, 2003**, and U.S. Provisional Application Serial No. 60/485,607, **filed July 7, 2003**.

Herzog was **published on 15 November 2003** (see p. 3483, bottom margin). According to the copy of the cover sheet provided by the Examiner, it was "**[p]republished online Jul 31, 2003**."

Thus, Herzog lacks priority over the present application.

Applicants respectfully submit that claim 64 fulfills the requirements of 35 U.S.C. §103(a), thereby placing this claim in condition for allowance, and request the Examiner's reconsideration accordingly.

CONCLUSION

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

Applicants hereby request a three-month extension of time for the Amendment and accompanying materials. If, however, a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an additional extension of time and the Commissioner is hereby authorized to charge our deposit account no. 04-1105 for the appropriate fee. Although it is not believed that any additional fee (in addition to the fee concurrently submitted) is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

Date: April 20, 2010

Kathryn A. Piffat, Ph.D., (Reg. No. 34,901)
Intellectual Property Practice Group
EDWARDS ANGELL PALMER & DODGE, LLP
P.O. Box 55874
Boston, Massachusetts 02205
Telephone: 617-239-0100

Customer No. 21874